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ScienceDirect
Journal of Photochemistry and Photobiology B: Biology 85 (2006) 198–204
Journal of Photochemistry and Photobiology B:Biology
www.elsevier.com/locate/jphotobiol

The objective assessment of lifetime cumulative ultraviolet exposure for determining melanoma risk

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Received 26 January 2006; received in revised form 24 July 2006; accepted 4 August 2006
Available online 11 September 2006

Abstract

Exposure to ultraviolet radiation has commonly been recognized as the most important environmental risk factor for melanoma. The measurement of UV exposure in humans, however, has proved challenging. Despite the general appreciation that an objective metric for individual UV exposure is needed to properly assess melanoma risk, little attention has been given to the issue of accuracy of UV exposure measurement. The present research utilized a GIS based historical UV exposure model (for which the accuracy of exposure estimates is known) and examined, in the case–control setting, the relative importance of UV exposure compared to self-reported time spent outdoors, in melanoma risk. UV estimates were coupled with residential histories of 820 representative melanoma cases among non-Hispanic white residents under 65 years of age from Los Angeles County and for 877 controls matched to cases by age, sex, race, and neighborhood of residence, to calculate the cumulative lifetime UV exposure and average annual UV exposure. For historical measures, when the participants resided outside the US, we also calculated UV estimates. While there was no increased risk of melanoma associated with self-reported time spent outdoors, the association between annual average UV exposure based on residential history and melanoma risk was substantial, as was the association between cumulative UV exposure based on residential history and melanoma. The time spent in outdoor activities appeared to have no significant effect on melanoma risk in any age strata, however, when adjusted for UV exposure based on residential history, time spent outdoors during young age significantly increased risk for melanoma. While there was some attenuation of risk when we excluded data from people resident overseas (as all other studies we are aware of have done), this did not significantly impact subsequent risk estimates of UV exposure on melanoma.
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Keywords: Sun exposure; Melanoma; Exposure assessment; Ultraviolet; GIS

1. Introduction

Exposure to ultraviolet radiation has long been recognized as the most important environmental risk factor for melanoma [1–5]. The early epidemiological evidence that solar radiation might play a role in the etiology of melanoma resulted from ecological studies that demonstrated that melanoma incidence varies by latitude and altitude worldwide [6–9]. Locations closer to the equator and at higher altitudes generally have higher melanoma incidence rates [6]. Exposures in early childhood may be most important [10,11] and there is some evidence that cumulative UV exposure and the time spent outdoors may increase melanoma risk [12].

The measurement and assessment of historical UV exposure, however, has proved challenging. Typically, the individual UV estimates are based on patient and control self-report of exposure and are therefore subject to substantial recall bias [13]. In an attempt to account for historical exposure, birthplace or previous residence along with mean annual hours of bright sunshine received at each location has been used as the metric of individual UV exposure

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doi:10.1016/j.jphotobiol.2006.08.002

[14]. However, this metric is not the best proxy for UV exposure because of the inconsistent relationship between incoming solar radiation and sunshine hours [15]. Fears et al. [12] is the first study we are aware of that estimated UV exposure at places of residence based on the actual UV measurements recorded by approximately 30 radiation stations across the continental USA. However, a principal limitation is that the accuracy of individual UV exposure estimates is unknown. The analysis relied on interpolation of data from a small imperfect measurement network and is subject to a degree of uncertainty (error), because the derived values are only estimates of the real values at a particular location [16]. Consequently, misclassification of exposures is likely to spuriously reduce effect estimates (assuming non-differential misclassification in cases and controls). Another potential problem is the lack of completeness, and/or compatibility of UV exposure data for residences outside the USA, which may adversely affect the estimates of cumulative lifetime exposure: for certain locations in the US, migrants are likely to have very different UV exposure potential in their home countries (which is more likely to have occurred in childhood) than those occurring in the US.

In studies of the role of UV exposure in melanoma to date little attention has been given to the issue of uncertainty (error) in individual exposure estimates. In an effort to improve accuracy of UV exposure measurement we [17] evaluated the performance accuracy of the Thiessen-polygon and Kriging interpolation procedures available in standard GIS packages, based on the magnitude and distribution of errors, and compared results with those of the ANUSPLIN routine [18] that runs outside typical GIS through a series of C++ and FORTRAN commands. The impetus for stepping outside the typical GIS toolbox and using ANUSPLIN was stimulated by the success of this procedure in predicting precipitation, temperature, and other climate variables while incorporating their spatial dependence on elevation [19–25]. The ANUSPLIN procedure utilized two FORTRAN programs: SPLINA and LAPGRD. The SPLINA program calculated predictions of global solar radiation using partial thin plate smoothing splines. This routine generated numerous diagnostics in addition to the surface coefficients that summarize the relationship between mean global solar radiation, latitude/longitude and elevation. LAPGRD combined these surface coefficients with the 30″ Digital Elevation Model (DEM) to estimate solar radiation values at each approximately 1 km^2 DEM grid node. In comparison to the Thiessen Polygon and Kriging interpolation procedures ANUSPLIN produced the smallest root mean square error, smallest variance of error, and proved to generate as much as 11 times more accurate predictions [17].

In the present study, we used ANUSPLIN model predictions to build a GIS based historical UV exposure model and examine, in a case–control setting, the relative importance of UV exposure, compared to self-reported time spent outdoors in melanoma etiology. As a part of this endeavor, we assessed the impact of missing data from overseas, the impact of self-reported time spent outdoors, the impact of simple measurement of our imputed UV measure, and the impact of adjusting self-reported time outdoors by imputed UV measurement on melanoma risk.

2. Methods

2.1. Case–control dataset

The case–control dataset included 820 melanoma cases among white non-Latino residents under 65 years of age that were recruited from the Los Angeles County Cancer Surveillance Program (CSP), a population-based cancer registry since 1972 [26]. Complete details of the ascertainment of cases and controls are provided elsewhere [27]. Cases over 65 years old were excluded to minimize the recall bias of events occurring in young age. Controls included 877 individuals that were identified from the residential community of the cases using an algorithm for walking neighborhoods and identifying control subjects by the location of their residence. Controls were matched to cases for ethnicity (white non-Latino), age (±5 years) and gender. An in-person interview for each case and matched control was conducted [27].

From the structured interview we ascertained:

(1) residential history from birth to time of interview recorded as county or country (if outside USA) of residence;
(2) time spent at each residence reported (in years); and
(3) time spent in outdoor activity – an average number of days per year of outdoor activity during age periods 15–24, 24–44 and older than 45 years of age.

2.2. The UV exposure dataset

The National Solar Radiation Database (NSRAD) produced by the National Renewable Energy Laboratory (NREL) under the Department of Energy's (DOE) Resource Assessment Program served as the data source for interpolation of UV exposure at unsampled locations. NSRAD contains statistical summaries computed from hourly data for 239 US radiation stations for the period 1961–1990. The statistics include monthly, yearly, and 30-year average daily direct, diffuse, and global horizontal solar radiation measures and standard deviations.

The estimates of UV exposure for continental US used in the present research comprise county level ANSPLIN model predictions of the 30-year AVerage daily total GLObal solar radiation (AVGLO) defined as the total amount of direct and diffuse solar radiation in Wh/m^2 received on a horizontal surface (Fig. 1). The decision to use 30-year average AVGLO measures was based on an initial analysis of temporal variability that showed no statistically significant difference in AVGLO measurements between the three

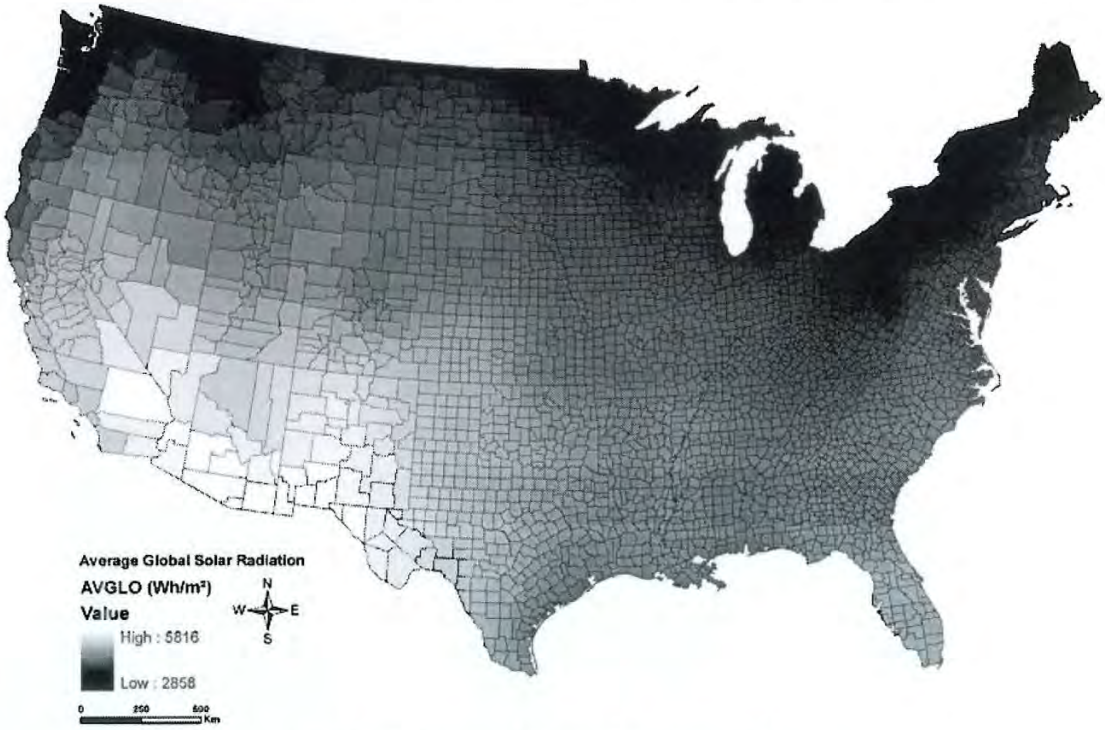

Fig. 1. UV exposure by county in continental USA.

10-year periods embedded in the 1961–1990 data summaries for each radiation station [17].

The AVGLO measurements were adopted and tested as a proxy for UV, because the spatial distribution and quantity of AVGLO data was larger and more complete than any UV database available for interpolation. Monthly UVB data from the Surface Radiation Budget Network (SURFRAD) stations of the National Oceanic and Atmospheric Administration (NOAA) were used for comparison with AVGLO data at similar or nearby locations to see how well the variability in AVGLO mimicked the variability in UV. The large positive correlation coefficients ($r^2 > 0.97$) obtained indicated that the variability of global radiation measurements mimics the variations in UV at similar locations and could, therefore, be used as a proxy for UV [17].

The estimates of UV exposure for the foreign residences were obtained from NASA [28]. The NASA dataset includes 10-year (1983–1993) AVGLO measurements in units comparable to the NSRAD dataset (Wh/m^2). The two exposure datasets were tested for comparability by calculating the correlation coefficient between 30 randomly selected AVGLO values for the continental USA and NASA measurements at the same geographic locations for the same time period.

2.3. The historical UV exposure model

The historical UV exposure model was generated in a geographic information system (GIS) environment, using ESRI's ArcGIS 9 (Environmental Systems Research Institute, Inc., Redlands, CA). The method resulted in the spatio-temporal linkage of several groups of independent datasets, including: the geographic coordinates of different residences of study participants, time at each residence, and corresponding UV exposure. Initially, the geographic coordinates were identified by their unique county FIPS (unique county identifier) and country names through a series of overlay operations on the multiple point coverages. Subsequently, this information was linked to the time spent at each residence and to UV exposure data sets using multiple join operations.

The UV exposure measurements for the missing residential records were estimated by averaging exposure measurements at all known locations. Two measures of UV exposure were calculated, the cumulative lifetime exposure and the average annual exposure. To get the first measurement the UV exposure at each residence was multiplied by time spent at that residence and summed. The average annual UV exposure was obtained by averaging cumulative exposure over lifetimes.

2.4. Statistical analysis

The statistical analyses were performed in SAS version 9.0. Two-sided p-values less than 0.05 were considered to be significant in the analyses. Conditional logistic regression was used to estimate odds ratios for melanoma, which account for the matching variables, age, sex and socioeconomic status. Cumulative lifetime exposure was categorized using an equal interval scale as <150,000; 150,000–200,000; 200,000–250,000; and $\geqslant$250,000 Wh/m^2. The categorical

cut-point for average annual UV exposure was based on tertiles of annual average exposure among controls over 45 years old within age strata. We used only 45+ age group here because young have less chance for exposure. The analysis of time spend in outdoor activity used three age-specific categories (15–24, 24–44 and older than 45 years of age) because exposure in young age is thought to be important. Essentially, the cut-points for all age-specific analyses are determined from the tertiles of values in the corresponding control series (i.e., the same age range of controls). The self-reported time spent in outdoor activity was categorized arbitrarily using an equal interval scale as 0–50, 51–100, 101–200 and more than 200 days per year.

We focus here on the potential for improvement over self-reported time spent outdoors that the objective UV measure determined by the ANUSPLIN method provides. Therefore, we have not provided a full model of melanoma risk factors included in the case–control study (and reported elsewhere). However, the matched design accounts for age, sex, and socioeconomic factors in the analyses presented.

3. Results

3.1. Residential histories and comparability of UV exposure datasets

The reported residential histories of study participants were relatively complete with only 6% of the participants missing more than two residential records. The correlation analysis indicated that the NSRAD and NASA datasets are comparable ($r = 0.98$) and could therefore be used concurrently in this research to generate the historical UV exposure model.

3.2. Time outdoors, cumulative exposure, and average annual exposure

Table 1 presents odd ratios for melanoma that were calculated based on the average number of days of outdoor activity per year for all ages and for the participants that were older than 45 years of age. The results suggest that the number of days of outdoor activity alone is not significantly associated with melanoma in each age strata.

The results of analysis of the association between UV exposure and melanoma risk suggested that the cumulative lifetime UV exposure alone had a significant effect ($p < 0.05$) on melanoma risk, as indicated in Table 2a. Similarly, the association between the annual average UV exposure alone and melanoma is significant in young and mid age strata (15–24 and 25–44 years of age) (Table 2b).

The time spent in outdoor activity when adjusted for UV exposure, in early age (15–24 years of age) significantly increases risk for melanoma ($p < 0.05$) (Table 3).

4. Discussion and conclusions

UV exposure is critical in melanoma etiology; however, its measurement and assessment has proved challenging. Measurement of UV exposure to specific body sites on humans has been accomplished with personal passive UV dosimeters [29], which quantify the distribution and the fraction of the ambient UV radiant exposure on a horizontal plane. Personal dosimetry has been used to measure solar

Table 1
Association between days of outdoor activity and melanoma risk

# Days/Yr. Outdoor	Age 45+			All ages		
	Case–control	OR	95% CI	Case–control	OR	95% CI
Age 15–24						
≤50	25/35	1		45/57	1	
51–100	45/51	1.19	0.61–2.32	80/92	1.08	0.65–1.80
101–200	123/118	1.42	0.79–2.55	223/223	1.25	0.80–1.95
>200	142/163	1.26	0.70–2.28	305/335	1.11	0.72–1.71
Missing	6/2					
Trend			$p = 0.48$			$p = 0.76$
Age 25–44						
≤50	87/97	1		175/175	1	
51–100	92/98	1.19	0.79–1.80	173/189	0.95	0.71–1.27
101–200	111/113	1.19	0.79–1.80	189/188	1.06	0.79–1.44
>200	50/58	1.03	0.63–1.71	96/124	0.80	0.56–1.13
Missing	1/3			28/33		
Trend			$p = 0.70$			$p = 0.44$
Age 45+						
≤50	104/104	1		108/111	1	
51–100	85/103	0.91	0.60–1.38	89/104	0.94	0.62–1.42
101–200	95/101	0.94	0.62–1.42	98/103	1.03	0.69–1.53
>200	54/60	0.98	0.61–1.59	55/65	1.04	0.65–1.66
Missing	3/1			311/326		
Trend			$p = 0.99$			$p = 0.84$

Table 2a
Association between lifetime cumulative UV exposure and melanoma risk

Cumulative exposure (Wh/m^2)	All ages (US + Overseas)			All ages (US residences only)		
	Case–control	OR	95% CI	Case–control	OR	95% CI
<150,000	118/143	1		138/202	1	
150,000–200,000	160/174	1.62	0.99–2.67	169/159	2.16	1.42–3.28
200,000–250,000	168/201	2.64	1.29–5.39	163/182	2.59	1.53–4.38
⩾250,000	215/191	6.01	2.64–13.69	191/166	4.34	2.43–7.75
p-Value			<0.0001			<0.0001

Table 2b
Association between annual average UV exposure and melanoma risk

	45+			Everybody all ages (Overseas + US)			All ages (US only)		
	Case–control	OR	95% CI	Case–control	OR	95% CI	Case–control	OR	95% CI
Annual average exposure 15–24									
<4043	92/122	1		124/174	1		61/80	1	
4043–4840	107/124	1.23	0.81–1.87	182/202	1.33	0.96–1.84	101/119	1.16	0.82–1.63
⩾4840	142/123	1.74	1.15–2.63	355/333	1.65	1.21–2.24	286/245	1.51	1.10–2.08
Missing									
p-Value			$P = 0.0209$			$P = 0.0052$			$p = 0.0185$
			Trend $p = 0.0060$			Trend $p = 0.0012$			$P = 0.0053$
Annual average exposure 25–44									
<4736	67/122	1		94/168	1		41/75	1	
4736–5080	121/116	1.91	1.27–2.88	190/178	1.961	1.40–2.75	113/95	2.21	1.52–3.21
⩾5080	153/131	2.29	1.50–3.49	344/326	2.015	1.46–2.78	263/242	1.99	1.40–2.82
Missing				33/37			31/32		
p-Value			$P = 0.0002$			$P < 0.0001$			$P < 0.0001$
			Trend $p = 0.0001$			Trend $p = 0.0012$			Trend $p = 0.0026$
Annual average exposure 44+									
<5080	31/43	1		31/43	1		17/17	1	
⩾5080	310/326	1.20	0.72–2.02	310/326	1.203	0.72–2.02	175/176	1.11	0.64–1.92
Missing				320/340			256/251		
p-Value			$P = 0.48$			$P = 0.48$			$P = 0.71$

Categorical cut-point is based on tertiles of annual average exposure among controls over 45 years old within age strata.

UV radiant exposures in infants and small children [30], outdoor workers [31–33], school-children [33,34], home-workers [33,35] and during recreational activities [36]. While this approach may be useful for measuring current individual exposures, it is not able to measure past (early childhood) exposure, or cumulative lifetime exposure.

The impact of historical exposure in case–control studies has typically been assessed by self-report. The drawback in this subjective approach to UV exposure assessment is that results may be subject to recall bias. For example, if cases recalled their sun exposure in a biased fashion related to their knowledge of subsequent risk for melanoma, we might expect them also to overestimate their sun exposure at the site of their melanoma, compared with exposure at non-melanoma-affected anatomic sites. This has been the case for melanoma of the face/scalp/ neck for the reporting of sunburn in childhood [13].

The lack of objective individual UV exposure measurement has been a persistent obstacle to establishing solid evidence for the links between UV exposure and melanoma. Fears et al. [12] and Solomon et al. [37] are the only studies we are aware of that have attempted to measure lifetime UV exposure objectively. The former study used a small, imperfect UVB network to generate exposure estimates, while the later study used satellite data recorded over the relatively short time period. In each instance, the primary limitation of the method is that no attention was given to uncertainty (error) in the individual UV estimates when these might be expected to be relatively large given the sparse networks used and anticipated geographic variability in UV exposure. In our study we developed a GIS-based historical UV exposure model for which the accuracy of exposure measures is known and used this model to facilitate the objective assessment of lifetime cumulative UV exposure.

In our study, self-report of time spent in outdoor activities had no significant effect on melanoma risk in any age strata, however, when adjusted for UV exposure the time spent outdoors during young age (15–24) significantly increased risk for melanoma. While there was some attenuation of risk when we excluded data from people resident overseas (as all other studies we are aware of have done), this did not significantly impact subsequent risk estimates of UV on melanoma. These results imply that before adjustment for UV exposure, self-reported time spent outdoors was subject to random misclassification, which

Table 3
Association between UV adjusted time spent outdoors and melanoma risk

	45+			Everybody all ages (Overseas + US)			All ages (US only)		
	Case–control	OR	95% CI	Case–control	OR	95% CI	Case–control	OR	95% CI
UV adjusted outdoor 15–24									
<558,800	90/121	1		166/209	1		122/128	1	
558,800–1,042,671	123/124	1.33	0.91–1.94	217/222	1.20	0.91–1.58	144/129	1.09	0.82–1.46
⩾1,042,671	122/122	1.55	1.03–2.32	268/276	1.20	0.91–1.59	176/186	1.03	0.76–1.38
Missing	6/2			10/2			6/1		
p-Value			$P = 0.0955$			$P = 0.36$			$P = 0.83$
			Trend $p = 0.0333$			Trend $p = 0.22$			Trend $p = 0.89$
UV adjusted outdoor 25–44									
<294,330	110/120	1		212/210	1		143/137	1	
294,330–645,333	125/125	1.21	0.83–1.78	226/231	0.993	0.75–1.31	154/137	0.99	0.75–1.32
⩾645,333	105/121	0.99	0.67–1.46	186/228	0.819	0.62–1.09	117/137	0.82	0.61–1.09
Missing	1/3			37/40			34/33		
p-Value			$P = 0.74$			$P = 0.29$			$P = 0.27$
			Trend $p = 0.61$			Trend $p = 0.17$			Trend $p = 0.16$
UV adjusted outdoor 44+									
<299,720	123/121	1		123/121	1		76/63	1	
299,720–609,600	99/120	0.86	0.59–1.26	99/120	0.86	0.59–1.26	48/59	0.85	0.58–1.24
⩾609,600	116/127	0.91	0.64–1.32	116/127	0.91	0.64–1.32	65/71	0.91	0.63–1.30
Missing	3/1			323/341			259/251		
p-Value			$P = 0.74$			$P = 0.74$			$P = 0.69$
			Trend $p = 0.61$			Trend $p = 0.61$			Trend $p = 0.58$

Categorical cut-point is based on tertiles of annual average exposure among controls over 45 years old within age strata.

biased results towards the null. However, after adjustment with an objective UV measure we were able to reduce the effect of random misclassification.

Our measure is still fairly crude (based on county of residence, the assumption that an average annual exposure reflects actual exposures), so we further conclude that additional random misclassification of UV exposure is likely to occur in studies of melanoma etiology, and that the true effects of UV exposure are likely to be far greater than we report here.

Our measure does not reflect the possibility that people might be more likely to spend time outdoors in their activities during times of the year when UV levels are high, or the possibility that those with melanoma are more likely to have participated in outdoor activities in childhood during the high UV season. We estimated that the difference between average summer and winter UV exposures is almost two times as great as the mean annual geographic variability in AVGLO.

The principal advantage of the historical UV exposure model used in this research is that it is relatively simple, the results are reproducible, and we have demonstrated that the method goes some way to reducing bias towards the null in effect estimates of UV exposure in melanoma risk. Melanoma case–control studies need to take residential history and UV exposure at residence into account, because it clearly is an effect modifier for outdoor exposures and melanoma risk. When looking at the effects of UV exposure on disease outcomes consideration of lifetime exposure and actual UV exposure at place of residence (for example in studies of the protective effects of UV exposure, and of UV exposure on other cancers) should be included.

Acknowledgements

Dr. Cockburn was supported in part by Federal funds from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. N01-PC-35139 and by Grant No. U55/CCU921930-02 from the Centers for Disease Control and Prevention. This work was supported in part by NIEHS grant 5P30 ES07048.

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